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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GUPTA, ANISH	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 12/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/928,832	GROFTE ET AL.	
	Examiner	Art Unit	
	Anish Gupta	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1201*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Specification

1. The disclosure is objected to because of the following informalities:

The disclosure does not contain a brief description of drawings as required by the MPEP 608.01(f).

Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 1-2, 11, 17, 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Fujisawa Pharm Co. LTD (JP 09143094).

The claims are drawn to a method of treating individuals suffering form liver disease, such as chronic hepatitis, by administering to an individual IGF-1.

The reference teaches a preventive and treating agent for serious hepatitis containing IGF-1 (see abstract). The reference states that IGLF or its derivative ha an activity of improving liver function interference in serious hepatitis (see abstract). The concentration used is about 1 mg/kg of IGF-1 (see abstract). This concentration qualifies as more than 25 micrograms per day/kg of claim 17. Therefore, the reference anticipates the claimed invention.

2. Claims 1, 8-10, 14-16, 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Inaba et al. (J. Parent. And Enteral Nut.) and Lautt et al.

The claims are drawn to a method of treating individuals suffering form liver disease, such as chronic hepatitis, by administering to an individual IGF-1.

Inaba et al. teaches that the administration of IGF-1 exerted beneficial effects on systemic immunity after surgery in the setting of chronic liver injury (see page abstract and page 61). The reference discloses that rats were administered .05% TAA (thioacetamide) for six months to induce chronic liver injury (see page 56, Induction of Chronic liver injury). At this level, .05% TAA for six months, hepatic fibrosis or the early stages of liver cirrhosis was observed, thereby meeting the limitations of claims 8-10 in the instant application (see page 59). Inaba et al. goes on to teach that IGF-1 was administered at 4mg/kg/d for 3 days (see page 59). This meets the limitation of claim 17 since the claim allows for more than 25 micrograms per day/kg. An abnormality low level of circulating IGF-1 is observed in liver disease, thus meeting the limitation of claim 16 (see page 59). Inaba et al. states that IGF-1 was effective in preventing the translocation of bacteria and endotoxin by preserving the gut mucosa both anatomically and functionally (see page 61). Further, IGF-1 increased splenic weight after gastrectomy in the rat model (see page 61). Further, exogenous IGF-1 significantly improved postoperative whole-body protein turnover. It is theorized that IGF-1 infusion inhibits protein breakdown rathar than stimulating protein synthesis in food deprived rates (see page 60). Inaba et al. concludes that exogenous IGFL exerts beneficial effects on rats with chronic liver diseases (See abstract). Lautt et al. states that individuals with liver disease also show insulin resistance and insulin resistance leads to diabetes (see col. 1, lines 10-14). Thus, individual with liver disease, as a result of the prevalence of insulin resistance, would be diabetic.

As a final note, although multiple references have been used in the rejection of 102, this is permissible if the art is cited to show a characteristic not disclosed in the reference is inherent (see

MPEP 2131.01). Here, the reference of Lautt et al. was cited to show the presence of insulin resistance in patients with liver disease. Therefore, the reference anticipates the claim.

3. Claims 1, 8, 12-15, 17-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Picardi (J. of Hepatology) and Lautt et al.

The claims are drawn to a method of treating individuals suffering form liver disease, such as chronic hepatitis, by administering to an individual IGF-1.

Picardi teaches that patients with liver cirrhosis, derangements in the intermediary metabolism involving a variety of biochemical pathways lead to progressive deterioration of the nutritional state resembling protein-calorie malnutrition or starvation (see page 191). Picardi discloses that such disturbances were seen in the early stages of cirrhosis in rats and were treated with low dosage of IGF-I (see abstract). The IGF used is recombinant human IGF-I, thereby meeting the limitation of claim 19 (see page 192 and 193). Picardi discloses that at a dosage of 20 micrograms/Kg/day, thus meeting the limitation of claim 17 and 18, IGF-I reversed nutritional alterations hat are seen in cirrhotic rats, such as diminished food intake and food conversion efficiency, decrease in N-retention and impaired incorporation of dietary N into muscle (see page 198). The administration of IGF-1 stimulated food intake, thereby improving the body weight gain (see page 199). Further, the N balance after 5 experimental days, which was reduced in untreated cirrhotic rats, returned to normal values in cirrhotic rats treated with rhIGF-I (see page 199). It is well established that IGF-1 inhibits muscle protein degradation in the fasting state, while stimulating protein synthesis in the fed state (see page 199). Dietary N, which was decreased in the liver of cirrhotic rats, improved in rats treated with rhIGF-I (see page 200). In light of all these effects, the

reference concludes IGF-I can be useful in the correction of malnutrition in patients with liver cirrhosis (see abstract and page 200). Lautt et al. states that individuals with liver disease also show insulin resistance and insulin resistance leads to diabetes (see col. 1, lines 10-14). Thus, individual with liver disease, as a result of the prevalence of insulin resistance, would be diabetic.

As a final note, although multiple references have been used in the rejection of 102, this is permissible if the art is cited to show a characteristic not disclosed in the reference is inherent (see MPEP 2131.01). Here, the reference of Lautt et al. was cited to show the presence of insulin resistance in patients with liver disease. Therefore, the reference anticipates the claim.

The reference, therefore anticipate the claims.

4. Claims 1-8, 17-19 are rejected under 35 U.S.C. 102(e) as being anticipated by Fyklund et al. (US 6034059) and Caregaro et al. and Castilla et al. and Lautt et al.

The claims are drawn to a method of treating individuals suffering form liver disease, such as chronic hepatitis, by administering to an individual IGF-1.

Fyklund et al. teaches the administration of IGF-1 to patients to treat the catabolic state in the patient (see abstract). The patient is disclosed to be humans (see col. 3, lines paragraph bridging col. 3-4). The reference disclose that IGF-1 is the complete amino acid sequence of natural human IGF1 and is made by recombinant technology, thus meeting the limitation of claim 19 (see paragraph bridging col. 2 and col. 3). It should be noted that acute liver disease is nothing more than the end stage of chronic liver disease. As such many of the symptoms associated with chronic liver disease are prevalent in acute liver disease. It is known in the art that protein energy malnutrition is prevalent in patients that have liver disease with low levels of IGF-1 (see Caregaro et al. on page 185-186 and Castilla et al. on page 1181). Fyklund et al. states that "[a]s the liver is the

major source of systemic IGF-1, acute or chronic liver disease will induce GH resistance. Thus authentic IGF-1 may be particularly valuable in acute hepatic failure where protein loading can be dangerous and in catabolic states associated with chronic liver disease" (See Col. 4, lines 5-14). This teaching meets the limitation of claims 3-4. Therefore, Fyklund et al.teaches the treatment of both acute and chronic liver disease, thereby meeting the limitation of claims 3 and 8. It should be noted that Applicants specification acknowledges this teaching of the US Patent (see page 6 of the instant specification). Fyklund et al. states that the dosage of IGF-1 is between .02-20 mg/kg/day (see col. 3, lines 31-32). A dosage of .02 mg/kg/day corresponds to 20 micrograms/kg/day and meets the limitation of claims 17 and 18. Further, Lautt et al. states that individuals with liver disease also show insulin resistance and insulin resistance leads to diabetes (see col. 1, lines 10-14). Thus, individual with liver disease, as a result of the prevalence of insulin resistance, would be diabetic.

As a final note, although multiple references have been used in the rejection of 102, this is permissible if the art is cited to show a characteristic not disclosed in the reference is inherent (see MPEP 2131.01). Here, the reference of Lautt et al. was cited to show the presence of insulin resistance in patients with liver disease and Caregaro et al. and Castilla et al. were shown to illustrate that individuals with liver disease have low IGF-1 and show signs of malnutrition. Therefore, the reference anticipates the claim.

The reference anticipates the claimed invention.

5. Claims 1-8, 17-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Fyklund et al. (WO 92/03154) and Caregaro et al. and Castilla et al.

The claims are drawn to a method of treating individuals suffering form liver disease, such as chronic hepatitis, by administering to an individual IGF-1.

Fyklund et al. teaches the administration of IGF-1 to patients to treat the catabolic state in the patient (see abstract). The patient is disclosed to be humans (see page). Fyklund et al. disclose that IGF-1 is the complete amino acid sequence of natural human IGF1 and is made by recombinant technology, thus meeting the limitation of claim 19 (see page 4). It should be noted that acute liver disease is nothing more than the end stage of chronic liver disease. As such many of the symptoms associated with chronic liver disease are prevalent in acute liver disease. It is known in the art that protein energy malnutrition is prevalent in patients that have liver disease with low level of IGF-1 (see Caregaro et al. on page 185 and 186 and Castilla et al. on page 1181). Fyklund et al. states that "[a]s the liver is the major source of systemic IGF-1, acute or chronic liver disease will induce GH resistance. Thus authentic IGF-1 may be particularly valuable in acute hepatic failure where protein loading can be dangerous and in catabolic states associated with chronic liver disease" (See page 6). Therefore, Fyklund et al. teaches the treatment of both acute and chronic liver disease, thereby meeting the limitation of claims 3 and 8. Fyklund et al. states that the dosage of IGF-1 is between .02-20 mg/kg/day. A dosage of .02 mg/kg/day corresponds to 20 micrograms/kg/day and meets the limitation of claims 17 and 18 (see page 5). Further, Lautt et al. states that individuals with liver disease also show insulin resistance and insulin resistance leads to diabetes (see col. 1, lines 10-14). Thus, individual with liver disease, as a result of the prevalence of insulin resistance, would be diabetic.

As a final note, although multiple references have been used in the rejection of 102, this is permissible if the art is cited to show a characteristic not disclosed in the reference is inherent (see MPEP 2131.01). Here, the reference of Lautt et al. was cited to show the presence of insulin

resistance in patients with liver disease and Caregaro et al. and Castilla et al. were shown to illustrate that indivudals with liver disease have low IGF-1 and show signs of malnutrition. Therefore, the reference anticipates the claim.

The reference anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 20-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fryklund et al. (US6034059) or Fryklund et al. (WO9203154) and Caregaro et al., Castilla et al. and Lautt et al.

7. as applied to claims 1-8, 17-19 above, and further in view of Shirley et al. (WO 99/240632) and Clark (US 5187151),

Te claims are drawn to a method of treating individuals suffering form liver disease, such as chronic hepatitis, by administering to an individual IGF-1.

The reference of Fyklund et al. have been discussed supra. The reference also discloses a mode of administration includes subcutaneous or intramuscularly injection (see col. 3, lines 35-36 in US Patent and page 5 in the WO reference). The difference between the prior art and the instant application is that the reference does not teach the administration of an IGF binding protein, such as those listed in claims 20 and 21.

However, the reference of Shirley et al. teach that administration of IGF-1 is effective in treating acute and chronic conditions such as acute and chronic liver failure (see page 18, lines 13-16). Note that the primary reference also teaches the treatment of acute and chronic liver failure with IGF-1. The reference further states that IGF-1 can combined with any of the IGF-1 binding protein (IGFBP) (see page 15, lines 32-33). The IGF-1 binding protein can be any of the binding protein (see page 15, lines 32-33). The reference of Clark et al. teach that IGFBP produces a greater anabolic response for IGF-1 when combination therapy is used when compared to IGF-1 therapy alone (see abstract). The reference goes on to teach that IGFBP blocks hypoglycemia but not the anabolic effect of IGF-1 so that large doses of IGF-1 can be given without the risk of acute hypoglycemia (see col. 4, lines 50-54). Further, IGFBP allows for the administration of IGF-1 via subcutaneous route and have the desired anabolic effect, including states of nutritional stress. IGF-1 is relatively inactive when inactive when administered alone via subcutaneous route (see col. 4, lines 54-58). Note that the instant application's preferred route of administration is subcutaneous (see page 59 of the instant specification) and Fyklund et al. teach the administration via subcutaneous routes. The reference teaches that the positive effects of IGFBP is observed with any IGFBP, including IGFBP-1, IGFBP-2, IGFBP-3, IGFBP-4, IGFBP-5, and IGFBP-6 (see col. 6,

lines 6-21). Therefore it would have been obvious to combine IGF-1 and IGFBP because the prior art teaches the combination of IGF-1 and IGFBP to treat acute or chronic liver failure. Further, one would be motivated to combine IGF-1 and IGFBP because IGFBP allows IGF-1 to be administered via subcutaneous routes, allows for IGF-1 to be administered without having resulting in hypoglycemia, and allows the IGF-1 to have a greater anabolic response.

8. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Inaba et al. (J. Parent. And Enteral Nut.) and Lautt et al. as applied to claims 1-8, 16, 17 above, and further in view of Shirley et al. (WO 99/240632) and Clark (US 5187151).

The claims are drawn to a method of treating individuals suffering form liver disease, such as chronic hepatitis, by administering to an individual IGF-1.

The reference of Inaba et al. has been discussed supra. The difference between the prior art and the instant application is that the reference does not teach the administration of an IGF binding protein, such as those listed in claims 22.

However, the reference of Shirley et al. teach that administration of IGF-1 is effective in treating acute and chronic conditions such as acute and chronic liver failure (see page 18, lines 13-16). Note that the primary reference also teaches the treatment of acute and chronic liver failure with IGF-1. The reference further states that IGF-1 can combined with any of the IGF-1 binding protein (IGFBP) (see page 15, lines 32-33). The IGF-1 binding protein can be any of the binding protein (see page 15, lines 32-33). The reference of Clark et al. teach that IGFBP produces a greater anabolic response for IGF-1 when combination therapy is used when compared to IGF-1 therapy alone (see abstract). The reference goes on to teach that IGFBP blocks hypoglycemia but not the anabolic effect of IGF-1 so that large doses of IGF-1 can be given without the risk of acute

hypoglycemia (see col. 4, lines 50-54). The reference teaches that the positive effects of IGFBP is observed with any IGFBP, including IGFBP-1, IGFBP-2, IGFBP-3, IGFBP-4, IGFBP-5, and IGFBP-6 (see col. 6, lines 6-21). Therefore it would have been obvious to combine IGF-1 and IGFBP because the prior art teaches the combination of IGF-1 and IGFBP to treat acute or chronic liver failure. Further, one would be motivated to combine IGF-1 and IGFBP because IGFBP allows for IGF-1 to be administered without having resulting in hypoglycemia, and allows the IGF-1 to have a greater anabolic response.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (703) 308-4001. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback , can normally be reached on (703)306-3220. The fax phone number of this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Anish Gupta
12/10/03